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(54) Title: DOPAMINE D₄ RECEPTOR ANTAGONISTS AS TREATMENT FOR ATTENTION DEFICIT-HYPERACTIVITY DISORDER

(57) Abstract: A method of inhibiting motor hyperactivity in a mammal exhibiting the symptoms of attention deficit-hyperactivity disorder (ADHD) includes administering to a mammal a dopamine D₄ receptor-selective antagonist.

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DOPAMINE D₄ RECEPTOR ANTAGONISTS AS TREATMENT FOR
ATTENTION DEFICIT-HYPERACTIVITY DISORDER

This invention was made with support from the United States Government under USPHS (NIMH) Grant No. 1-R-01-MH-34006. The United States has certain rights in this invention.

Background of the Invention

The invention relates to the role of dopamine D₄ receptors in behavioral hyperactivity. In particular, it relates to treatments and therapies for inhibiting motor hyperactivity and attentional dysfunction associated with attention deficit-hyperactivity disorder (ADHD).

Attention deficit-hyperactivity disorder (ADHD) is a prevalent neuropsychiatric syndrome that affects 2%-5% of school-aged boys, an uncertain proportion of girls, and some adults. See R.A. Barkley, *Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment* (Guilford Press, New York, 1990). ADHD is characterized by excesses of hyperactive, inattentive and impulsive behavior. For several decades, the primary treatment available has been with psychostimulants for dopamine-enhancing effects, such as methylphenidate (Ritalin®) and amphetamines. Clinical use of these drugs is unsatisfactory owing to their short-lived benefits, risk of impaired sleep and

appetite, of abnormal movements, and of abuse and illicit trade. See Goldman *et al.*, *JAMA*, 279:1100 (1998).

An important action of stimulants is to enhance the functional activation of the amine neurotransmitter dopamine in the brain. See B.B.

- 5 Hoffman and R.J. Lefkowitz in *The Pharmacological Basis of Therapeutics*, Chapter 10, Eds. Goodman and Gilman, McGraw-Hill, New York (1996).

Dopamine (DA) is an important neurotransmitter involved in motor control, endocrine function, reward cognition and emotion. Dopamine modulates physiological processes through activation of five G-protein coupled receptors of the D₁-like (D₁ and D₅) and the D₂-like (D₂, D₃, and D₄) receptor families. See
10 K.A. Neve and R.L. Neve, in *The Dopamine Receptors*, K.A. Neve, R.L. Neve, Eds.; Humana Press, Totawa, New Jersey, 1997; pp. 27-76. D₄ receptors have received much attention, in part, because some atypical antipsychotics, notably clozapine, bind to D₄ receptors with higher affinity than to the more prevalent D₂
15 receptors. See H.H.M. Van Tol *et al.*, *Nature* 350:614 (1991); and Seeman *et al.* *Neuropsychopharmacology* 16:93 (1997).

Human D₄ receptors occur in multiple forms with 2-11 copies of a 16-amino acid (48 base pair) sequence in the putative third intracellular loop of the peptide sequence. See Neve and Neve, *supra*. Several recent genetic studies
20 suggest associations between polymorphic variants of the D₄ receptor gene (D4DR) and ADHD. These studies are inconclusive, with various studies producing evidence for and against such an association, but converging evidence

suggests that the D₄ receptor has a role in exploratory behavior and as a genetic susceptibility factor for attention deficit disorder.

Tarazi *et al.*, in "Dopamine D₄ receptors: significance for psychiatry at the millennium", *Molecular Psychiatry*, 4:529 (November 1999), identify a
5 number of D₄ receptor-selective antagonists and report on the behavioral effects of these agents in animal models for psychosis. Tarazi *et al.* report mixed results, with some antagonists showing an antipsychotic-like effect, while others did not.

Numerous investigations into the effects of selective D₄ receptor agonists and antagonists on a variety of physiological and neurological functions
10 have drawn a complex picture of the effects of D₄ receptor-selective drugs and no clear picture has emerged as to the role of the D₄ receptor in these processes. See Tarazi *et al.*, *supra*; Patel *et al.*, *J. Pharmacol. Exp. Ther.*, 283(2):636 (Nov 1997); Bristow *et al.*, *J. Pharmacol. Exp. Ther.*, 283(3):1256 (Dec 1997); Feldpausch *et al.*, *J. Pharmacol. Exp. Ther.*, 286(1):497 (July 1998; P.A.
15 Broderick and M.F. Piercey, *J. Neuro. Transm.*, 105(6-7):749 (1998); Sanner *et al.*, *Bioorg. Med. Chem. Lett.*, 8(7):725 (April 1998); Jentsch *et al.*, *Psychopharmacology (Berl)*, 142(1):78 (Feb 1999); Belliotti *et al.*, *J. Med. Chem.*, 42(25):5181 (Dec 1999); and Okuyama *et al.*, *Life Sci.*, 65(-):2109 (1999).

20

Summary of the Invention

The present invention is based on the discovery that motor hyperactivity can be dose-dependently reversed by D₄ receptor-selective antagonists.

The invention features a method of inhibiting motor hyperactivity in a mammal exhibiting the symptoms of attention deficit-hyperactivity disorder (ADHD). The method includes administering to a mammal a dopamine D₄ receptor-selective antagonist.

5 The D₄ receptor-selective antagonists are selected from the group consisting of PNU-101958, RBI-257, NGD-94-1, L-745,870, L-750,667, PD-172,938, PNU-101387G, S-18126, NRA-0045, CP-293,019, YM-43611 AND YM-50001, the structures of which are shown in Table 1. Preferred D₄ receptor-selective antagonist are CP-293,019 (7R,S-(4-fluoro-phenoxyethyl)-2-(5-fluoro-
10 pyrimidin-2-yl)-octahydropyrido[1,2-*a*]pyrazine) and L-745,870(3-{{[4-(4-chlorophenyl)piperazin-1-yl]methyl}-1H-pyrrolo[2,3-*b*]pyridine, based on their high selectivity for D₄ over D₂ receptors.

 The D₄ receptor antagonist is administered intramuscularly, intravenously or subcutaneously to the mammal, and may be administered
15 together with a pharmaceutically acceptable carrier. Preferred mammals include humans.

 D₄ receptor-selective antagonists are expected to be superior to the conventional therapies using psychostimulants in that they do not stimulate dopamine release or block its inactivation by reuptake or transport. This
20 expectation is supported by the observation that D₄ receptor-selective antagonists do not affect motor activity in healthy rats. See Bristow *et al.*, *supra*; and Okuyama *et al.*, *supra*.

Brief Description of the Drawing

The invention is described with reference to the figures, which are presented for the purpose of illustration only and are not intended to be limiting of the invention.

5 Figure 1 plots the locomotor activity of sham-lesioned (control) rats (○) and 6-OHDA-lesioned rats (●) over a 90 minute observation period for (A) Daytime activity, at 10:00-16:00h (N=23); and (B) Nocturnal activity, 22:00-04:00h (N=17).

10 Figure 2 shows the effect of psychostimulants in (A) 6-OHDA-lesioned rats (10:00-16:00h; N=14-23), and (B) sham-lesioned rats (10:00-16:00h, N=12) and is a plot of the locomotor activity of rats without psychostimulant (○), with administration of methylphenidate (●), and with administration of amphetamine (▽).

15 Figure 3 is a plot of percent increase in receptor binding vs. locomotor activity for D₂-like receptors (○) and D₄ receptors (●), which shows the relationship between motor hyperactivity and changes of dopamine receptor binding in CPu of 6-OHDA-lesioned rats analyzed by Spearman Rank Correlation for N=12.

20 Figure 4 is plot of the locomotor activity of 6-OHDA-lesioned rats over a 90 minute observation period without D₄ antagonist (○); and at a low dosage (●) and high dosage (▽) of CP-293,019 for (A) Daytime activity, 10:00-16:00h (N=23); and (B) Nocturnal activity, 22:00-04:00h (N=13).

Figure 5 is a plot of the locomotor activity of 6-OHDA-lesioned rats over a 90 minute observation period without antagonist (○); with L-745,870 (●), 10:00-16:00h(N=9).

Figure 6 is a plot of the locomotor activity of 6-OHDA-lesioned rats over a 90 minute observation period without D₄ agonist (○); and at a low dosage (●) and high dosage (▽) of CP-226,269, a selective D₄ receptor agonist, 10:00-16:00h (N=17).

Figure 7 is a plot of the locomotor activity of sham-lesioned rats over a 90 minute observation period without added drug (○); with CP-293, 019 (●) and with CP-226,269 (▽), 10:00-16:00h (N=17).

Figure 8 is a plot of the locomotor activity of 6-OHDA-lesioned rats over a 90 minute observation period without D₄ agonist (○); with methysergide (Δ) (2 mg/kg administered 30 min prior to testing), with CP-293,019(●) (30 mg/kg); and with both methysergide and CP-293,019 (▲), which shows the absence of an effect of methysergide pretreatment on motor-inhibiting effects.

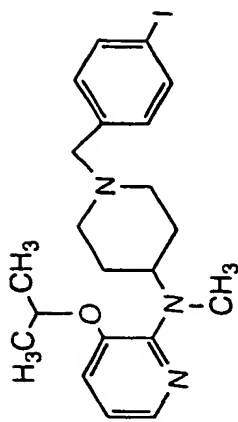
Detailed Description of the Invention

We have found that motor hyperactivity can be dose-dependently reversed by D₄ receptor-selective antagonists. D₄-selective agonist, in contrast, exacerbates lesion-induced hyperactivity. D₄ receptors in ADHD model animals were increased (up-regulated) even more than D₂ receptor, and in a manner that closely correlated with motor hyperactivity, indicating that D₄ receptor-selective antagonists should be useful in the treatment of ADHD.

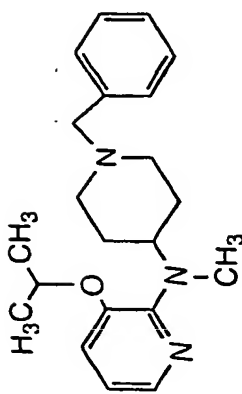
We have also found that the behavioral effects of the D₄ receptor-selective antagonists were not mediated by increased release of serotonin (5-hydroxytryptamine, 5-HT), an endogenous compound in the brain that may mediate the motor-inhibiting effects of stimulant drugs used in conventional
5 ADHD treatment. These findings indicate that selective D₄ receptor antagonists alleviate lesion-induced hyperactivity by a mechanism distinct from that of stimulant drugs.

Several selective D₄ receptor antagonists have been recently identified and may be used in the invention. See Tarazi *et al.*; Sanner *et al.*; Belliotti *et al.*;
10 and Okuyama *et al.*, *supra*. A non-limiting list of selective D₄ receptor antagonists is found in Table 1. A particularly preferred antagonist is 7R,S-(4-fluoro-phenoxyethyl)-2-(5-fluoro-pyrimidin-2-yl)-octahydro-pyrido[1,2-*a*]pyrazine, known as CP-293,019. CP-293,019 is a highly D₄ receptor-selective, full antagonist with more than 1000-times greater potency at D₄ receptors than at
15 D₂ or other DA receptors, with negligible affinity for non-dopaminergic receptors except for moderate or low potency at serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i = 150 and 500 μM, respectively). See Sanner *et al.*, *supra*. CP-293,019 can be used to treat humans with ADHD.

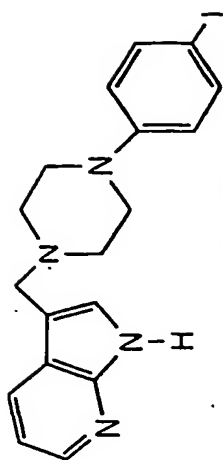
Another antagonist that can be used to treat humans with ADHD is 3-
20 {[4-(4-chlorophenyl)piperazin-1-yl]methyl}-1H-pyrrolo[2,3-b]pyridine known as L-745,870. L-745,870 is also a highly selective full antagonist for D₄ receptors. See Patel *et al.* *J. Pharmacol. Exp. Ther.* 283:636-647 (1997).



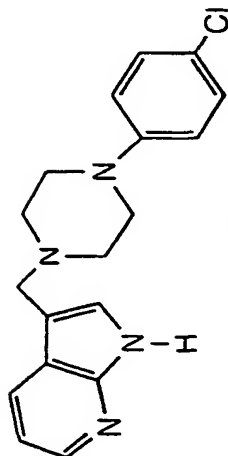
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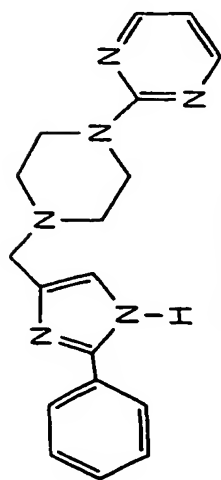
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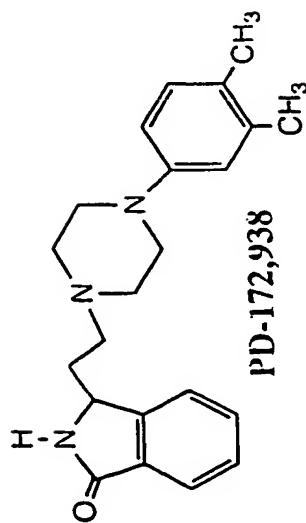
L-750,667



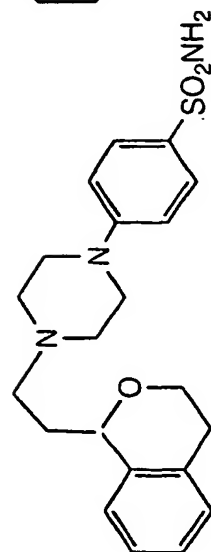
L-745,870



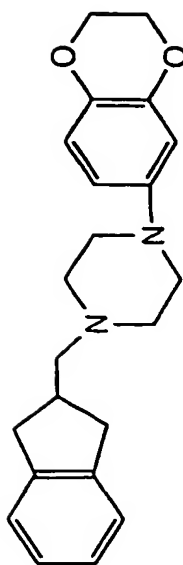
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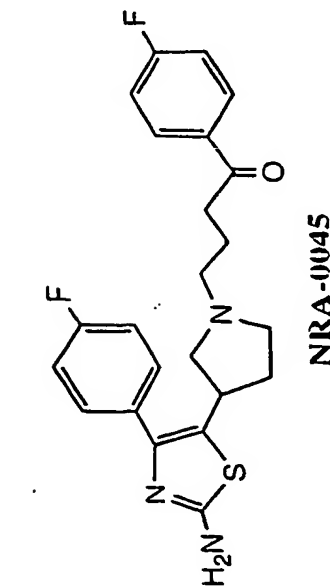
PD-172,938



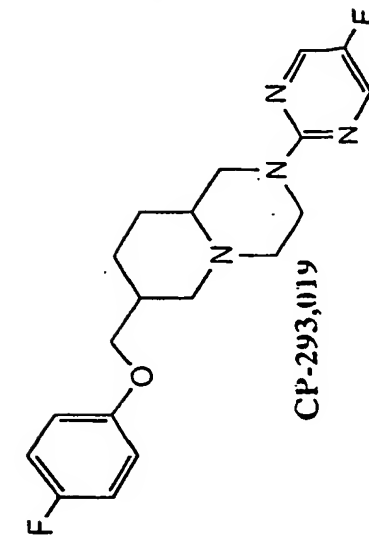
PNU-101,387G



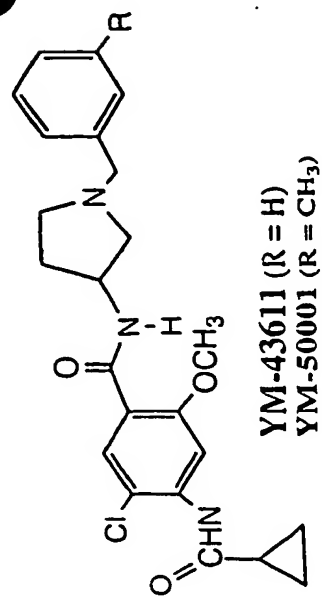
S 18126



NRA-0045



CP-293,019

YM-43611 (R = H)
YM-50001 (R = CH₃)

Suitable D₄ receptor-selective candidate antagonists for use in the treatment of motor hyperactivity may be readily identified using routine and well-established methods. For example, behavioral studies of juvenile rats with neonatal 6-hydroxydopamine (6-OHDA) lesions, as is described below, can be

5 used to screen drugs in order to identify candidate drugs for use in the method of the invention. Juvenile rats with neonatal 6-OHDA lesions of the brain that selectively destroy DA projections to the forebrain exhibit several characteristics that resemble the core symptoms of ADHD, most notably motor hyperactivity that occurs during the periadolescent period and gradually declines as lesioned rats

10 mature. The motor hyperactivity seems to be due to deficient adaption to environmental stimuli, and can be dose-dependently antagonized by psychostimulants that are commonly used to alleviate symptoms of ADHD. As a result, juvenile rats with neonatal 6-OHDA lesions are accepted as a laboratory model for ADHD.

15 The selective D₄ receptor antagonist may be administered at therapeutically effective levels using conventional methods. The antagonist may be administered orally, intramuscularly, intravenously or subcutaneously to the patient. The antagonist may be administered together with a pharmaceutically acceptable carrier or other excipients known in the pharmaceutical art.

20 The following example is to illustrate the invention; it is not meant to limit the invention in any way.

Example. Behavioral responses of 6-OHDA lesioned rats to D₄-selective drugs were investigated.

On postnatal day (PD) 5, male Sprague-Dawley rat pups randomly received intracisternal injections of vehicle ("sham-lesioned") (0.9% NaCl containing 0.1% ascorbic acid) or 6-OHDA hydrobromide ("lesioned") (100 µg free base) into the brain under hypothermal anesthesia at 45 min after pretreatment with desipramine hydrochloride (20 mg/kg free base) injected subcutaneously (s.c.). Lesions of DA in forebrain tissue sections were verified by quantifying DA transporter binding with [³H]GBR-12935 (1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine) by computed autoradiography at the completion of experiments as an indication of loss of DA nerve terminals in forebrain.

Behavioral effects of neonatal lesions were examined by monitoring locomotor activity at PD 21-30 in a novel environment to provoke exploratory activity. Rats were maintained under a 12-h artificial daylight/dark schedule (on, 07:00-19:00 h), with free access to tap-water and standard rat chow. Motor activity was automatically monitored for 90 min between PD 21 and 30, with a computer-controlled photobeam activity monitoring system (San Diego Instruments, San Diego, CA). Testing was carried out in a novel testing environment (17 x 8 x 8 inch transparent plastic cages with 4 x 8 horizontal infrared beams) between 10:00 and 16:00 h in the temporary absence of food and water. Test agents were dissolved in 0.9% saline or 35% 2-hydroxypropyl-β-cyclodextrin, and given intraperitoneally (i.p.) in randomized sequence immediately prior to testing. Sessions were separated by 48 hours. Some rats receiving CP-293,019 were pretreated with the serotonin receptor blocker

methysergide (2 mg/kg, i.p.) 30 min prior to behavioral testing. Breaking of consecutive photobeams was scored as locomotion.

Lesioned rats exhibited much higher spontaneous activity than sham-lesioned littermate controls during both daytime and nocturnal testing (Fig. 1A

5 and 1B). As is shown in Fig. 1A and 1B, motor activity of lesioned rats did not differ significantly from controls for the first 5-10 min of testing, but failed to

decline throughout the 90 min session, long after arousal in control rats had

greatly diminished. This temporal pattern indicated that lesioned rats are deficient in adaptation to behaviorally effective ambient stimuli in a novel environment.

10 As expected, hyperactivity in lesioned rats was reduced by (+)-amphetamine and (±)-methylphenidate (Fig. 2A), which is consistent with clinical administration of psychostimulants in patients with ADHD. In contrast to their motor-inhibiting effects in lesioned rats, both psychostimulants greatly increased motor activity in sham-lesioned controls (Fig. 2B).

15 Rats were sacrificed 2 days after the last behavioral testing for autoradiographic analysis of DA receptor density. Frozen coronal brain sections (10 µm) were prepared in a cryostat at -17°C, thaw-mounted on gelatin-coated microscopic slides and stored at -80°C until quantitative autoradiographic assays. D₂-like receptor binding was assayed with 1 nM [³H]nemonapride in the presence
20 of 0.5 µM 1,3-ditolylguanidine and 0.1 µM pindolol to block 5-HT_{1A} sites in the brain tissue. Nonspecific binding was determined with 10 µM 5(-)-sulpiride. D₄ receptor density was assayed similarly using [³H]nemonapride, but in the presence of raclopride in a concentration that selectively masks D₂ and D₃ but not D₄,

receptors. D₁-like receptors were assayed with 1.0 nM [³H]SCH-23390 in the presence of 40 nM ketanserin to mask 5-HT_{2A/2C} receptor sites. Nonspecific binding was determined with 1 μM cis-flupenthixol.

Neonatal 6-OHDA lesions significantly increased D₄ receptor binding
5 in caudate-putamen tissue (CPu; lateral: 40.3%; medial: 35.2%), but not in
nucleus accumbens (NAc) or prefrontal cerebral cortex (PFC). D₂-like
(D₂/D₃/D₄) receptor binding also was increased in CPu, and not in NAc and PFC
by the lesions. The magnitude of increase of D₂-like receptors (16.6% and 18.3%
in lateral and medial CPu, respectively) was about half of that of D₄ receptors. D₁
10 -like receptor binding was unchanged in CPu, NAc and PFC by neonatal 6-OHDA
lesions. These results are reported in Table 2, which shows the specific receptor
binding of sham and lesioned rats. Specific binding data are reported in fmol/mg
tissue ± SEM. Data indicated by [*] or [**] demonstrate a statistically significant
difference between binding for sham-lesioned and 6-OHDA lesioned rats.

Table 2. Effects of neonatal 6-OHDA lesions on dopamine receptor binding in rat forebrain.

	<u>D₁-like</u>		<u>D₂-like</u>		<u>D₄</u>	
	Sham	6-OHDA	Sham	6-OHDA	Sham	6-OHDA
CPu/Latera	253.6 ±	228.5 ±	194.3 ±	226.5 ±	20.6 ±	28.9 ±
1	13.7	11.6	9.8	7.2*	2.2	1.4**
CPu/Media	244.1 ±	233.4 ±	133.3 ±	157.7 ±	14.2 ±	19.2 ±
1	14.3	11.8	6.8	6.0*	1.5	1.7**
NAc	167.9 ±	173.9 ±	114.6 ±	102.2 ±	14.0 ±	15.0 ± 1.6
	10.4	9.7	8.2	6.5	1.2	
PFC	36.3 ± 2.4	39.0 ±	9.8 ± 0.4	10.3 ±	2.0 ± 0.4	2.0 ± 0.2
		2.3		0.5		

5 * By ANOVA: p<0.05

** By ANOVA: p<0.01

Lesion-induced hyperactivity was strongly correlated with increases in D₄ receptor binding in CPu in individual rats but not with increases in of D₂-like
10 receptors. This is illustrated graphically in Fig. 3.

To assess the functional significance of the up-regulated D₄ receptors for motor hyperactivity induced by neonatal lesions, behavioral effects of representative D₄ receptor antagonist and agonist drugs were examined. CP-293,019 was chosen for this study because it is a highly D₄ receptor-selective, full
15 antagonist with negligible affinity for non-dopaminergic receptors. When locomotor activity was measured as described above for sham- and 6-OHDA-

lesioned rats, the D₄ receptor antagonist demonstrated dose-dependent mitigation of lesion-induced hyperactivity (Fig. 4A). At a dose of 10 mg/kg (i.p.), motor activity in lesioned rats was inhibited by approximately 40%, and at 30 mg/kg, it was indistinguishable from sham-lesioned controls. Nocturnal hyperactivity (equivalent to daytime activity in humans) also was completely reversed by CP-293,019 at 30 mg/kg in lesioned rats (Fig. 4B).

Another highly D₄-selective antagonist L-745,870 was also examined. At a dose of 15mg/kg (i.p.), motor activity in lesioned rats was reversed to a level similar to that found in control rats (Fig. 5).

In striking contrast to the effects of CP-293,019 and L-745,870, a highly D₄-selective agonist, CP-226,269, produced dose-dependent exacerbation of lesion-induced hyperactivity (Fig. 6). Neither D₄-agent (agonist or antagonist) affected motor activity in sham-lesioned controls (Fig. 7). This result is in contrast to psychostimulants that increase hyperactivity in control rats. See Fig. 2B. These findings suggest that D₄ receptors may be functionally dormant under normal conditions, but activated by DA denervation at a critical developmental period.

In addition to blocking or reversing neuronal transport of DA, stimulant drugs also release 5-HT. In hyperactive juvenile rats with neonatal 6-OHDA lesions as well as in hyperactive DA-transporter genetic knockout mice, the motor-inhibiting effects of stimulants seem to be mediated by enhanced release of 5-HT. Therefore, we tested the possibility of interaction of D₄-selective antagonists with 5-HT neurotransmission by using methysergide, a broad-

spectrum 5-HT receptor antagonist. Pretreatment of 6-OHDA-lesioned rats with methysergide did not affect their motor responses to subsequent injection of CP-293,019 (Fig. 8), suggesting that the behavioral effects of the D₄ antagonists were not mediated by increased release of 5-HT. Methysergide alone failed to affect
5 lesion-induced hyperactivity, further indicating that the motor-inhibiting effects of D₄-selective antagonists in lesioned rats were not due to affinity for 5-HT receptors.

A contribution of D₂ receptor blockade to the behavioral effects of D₄-selective antagonists seems unlikely since this agent interacts very weakly at D₂
10 receptors. These findings indicated that D₄-selective antagonists antagonize lesion-induced hyperactivity by a mechanism distinct from that of stimulant drugs.

Those skilled in the art will recognize or be able to ascertain with no more than routine experimentation many equivalents to the specific embodiments of the invention described herein. All patents and publications referenced herein
15 are hereby incorporated in their entirety by reference.

We claim:

1. A method of inhibiting motor hyperactivity in a mammal exhibiting the symptoms of attention deficit-hyperactivity disorder, said method comprising administration to said mammal of a dopamine D₄ receptor-selective antagonist selected from the group consisting of PNU-101958, RBI-257, NGD-94-1, L-475,870, L-750,667, PD-172,938, PNU-101387G, S-18126, NRA-0045, CP-293,019, YM-43611 AND YM-50001.

2. The method of claim 1, wherein said D₄ receptor-selective antagonist is CP-293,019.

10

3. The method of claim 1, wherein said D₄ receptor-selective antagonist is PNU-101958.

4. The method of claim 1, wherein said D₄ receptor-selective antagonist is L-475,870.

15

5. The method of claims 1, 2, 3, 4, or 5, wherein said D₄ receptor antagonist is administered intramuscularly, intravenously or subcutaneously.

20

6. Use of a D₄ receptor-selective antagonist selected from the group consisting of PNU-101958, RBI-257, NGD-94-1, L-475,870, L-750,667, PD-172,938, PNU-101387G, S-18126, NRA-0045, CP-293,019, YM-43611 AND YM-50001 for the treatment of attention deficit-hyperactivity disorder.

5

7. The use according to claim 6, wherein said D₄ receptor-selective antagonist is CP-293,019.

8. The use according to claim 6, wherein said D₄ receptor-selective
10 antagonist is PNU-101958.

9. The use according to claim 6, wherein said D₄ receptor-selective antagonist is L-475,870.

15

Fig. 1A

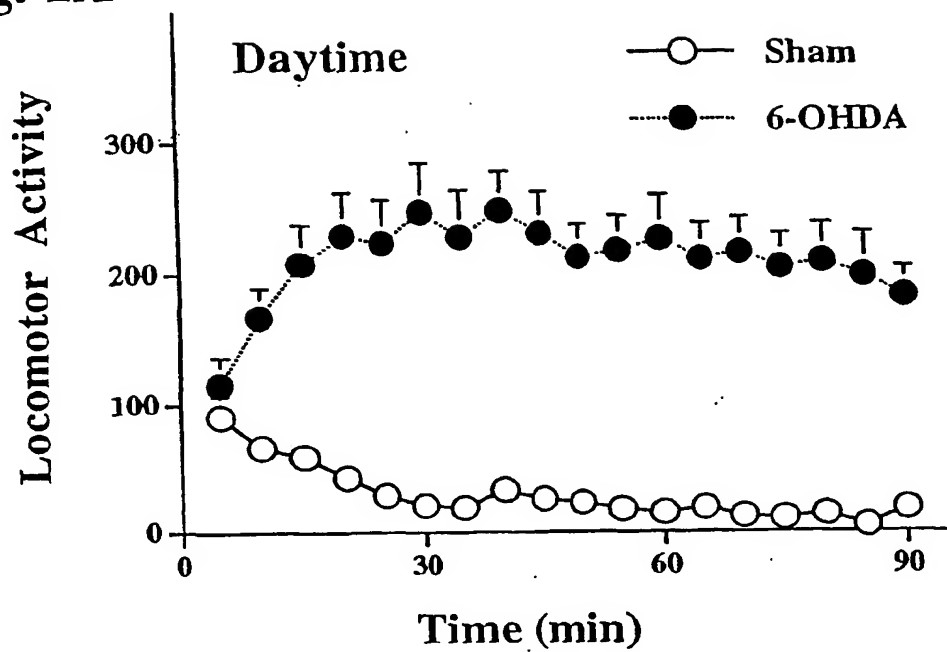


Fig. 1B

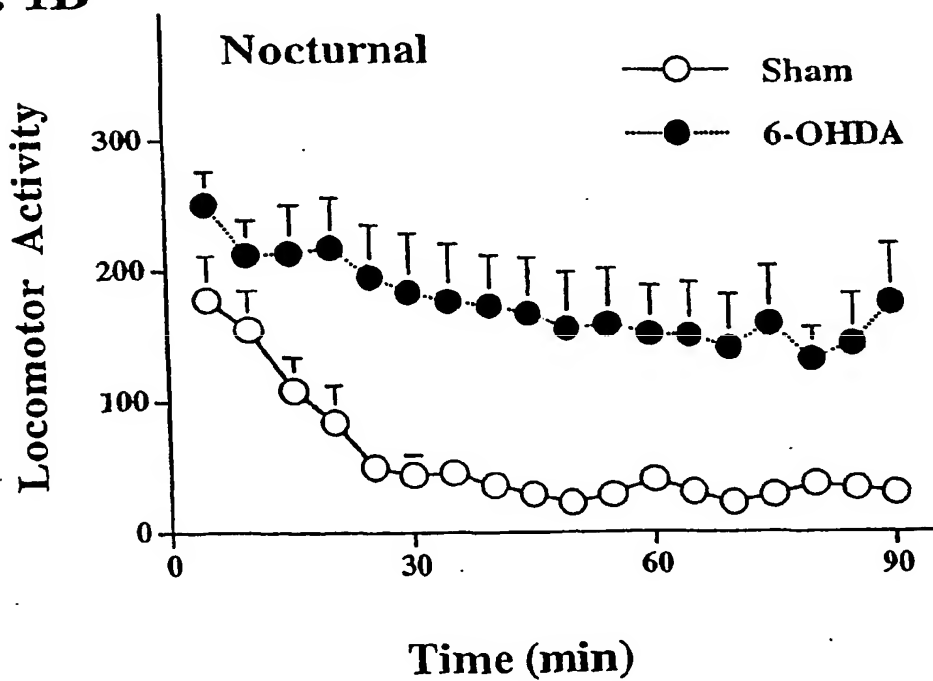


Fig. 2A

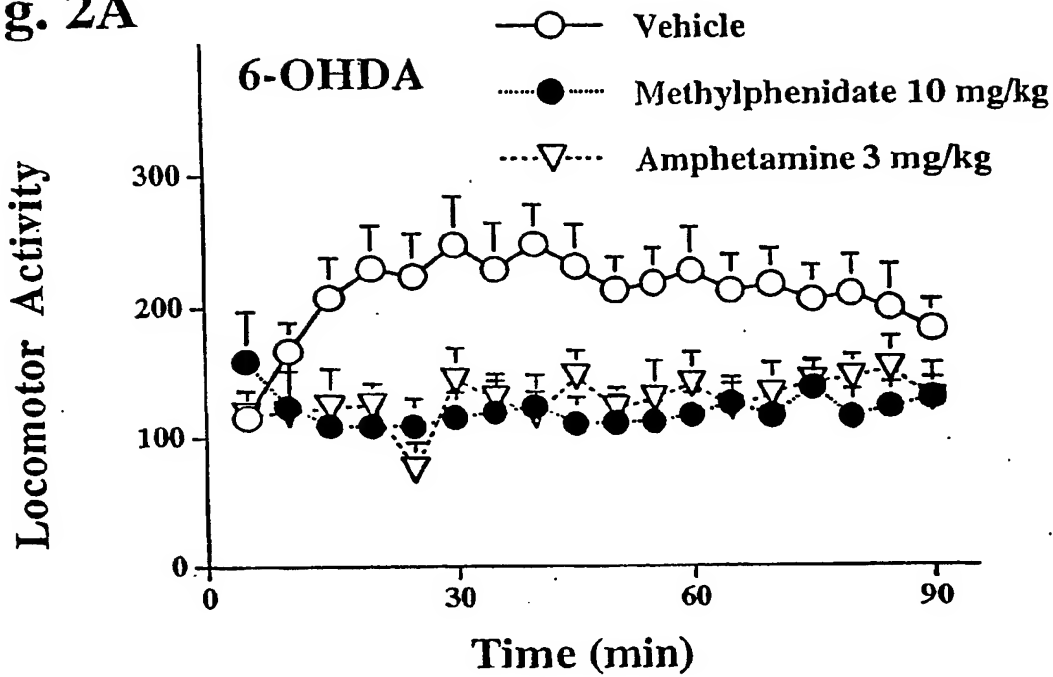


Fig. 2B

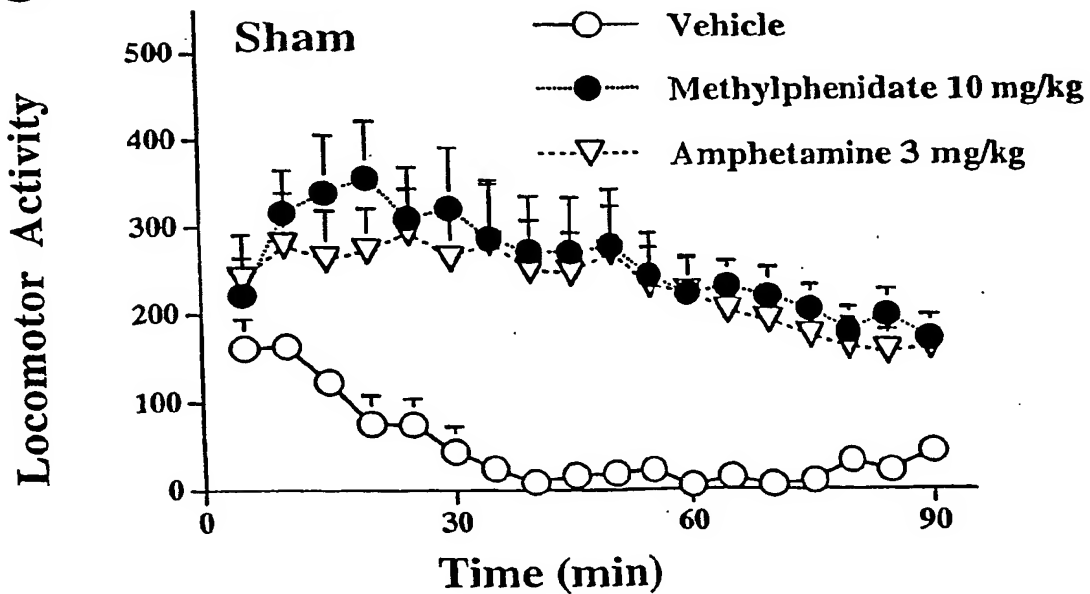


Fig. 3

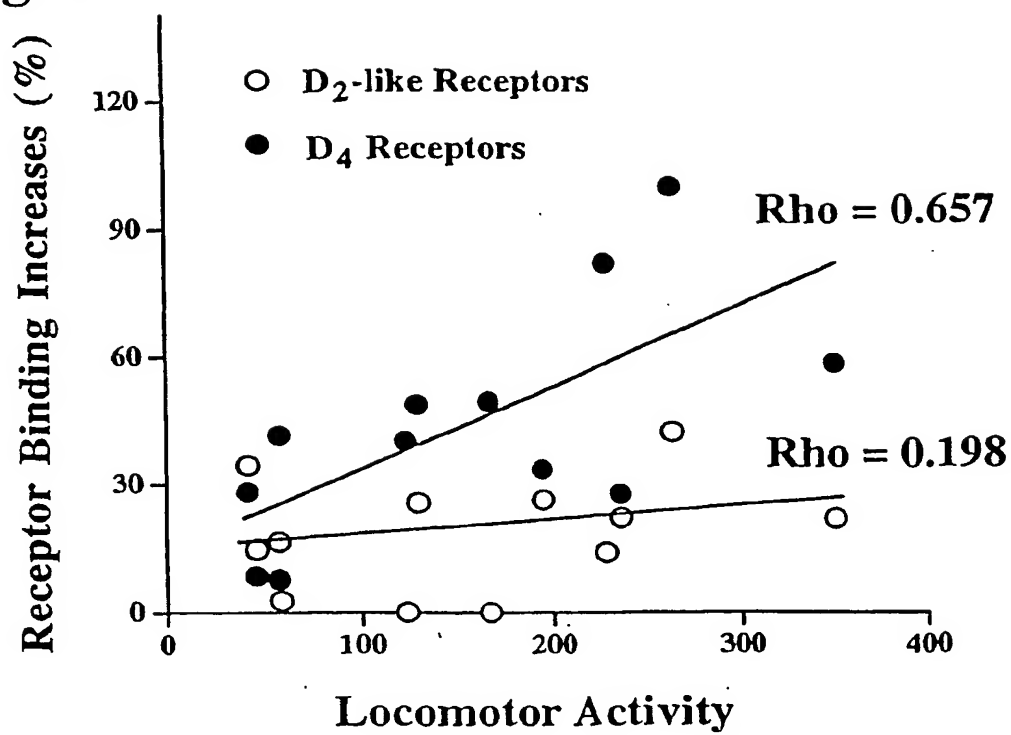


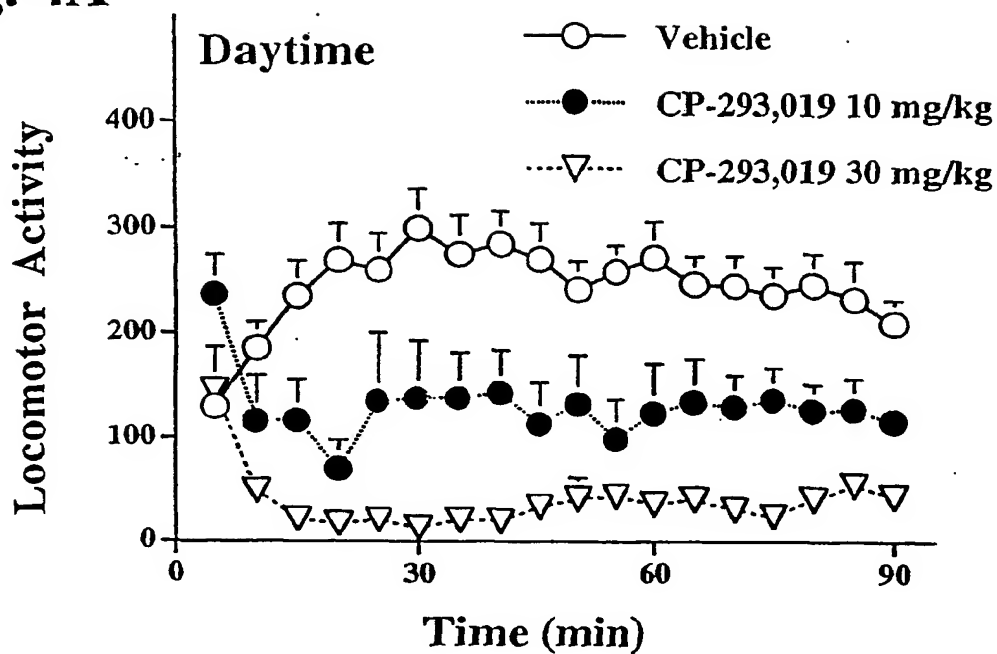
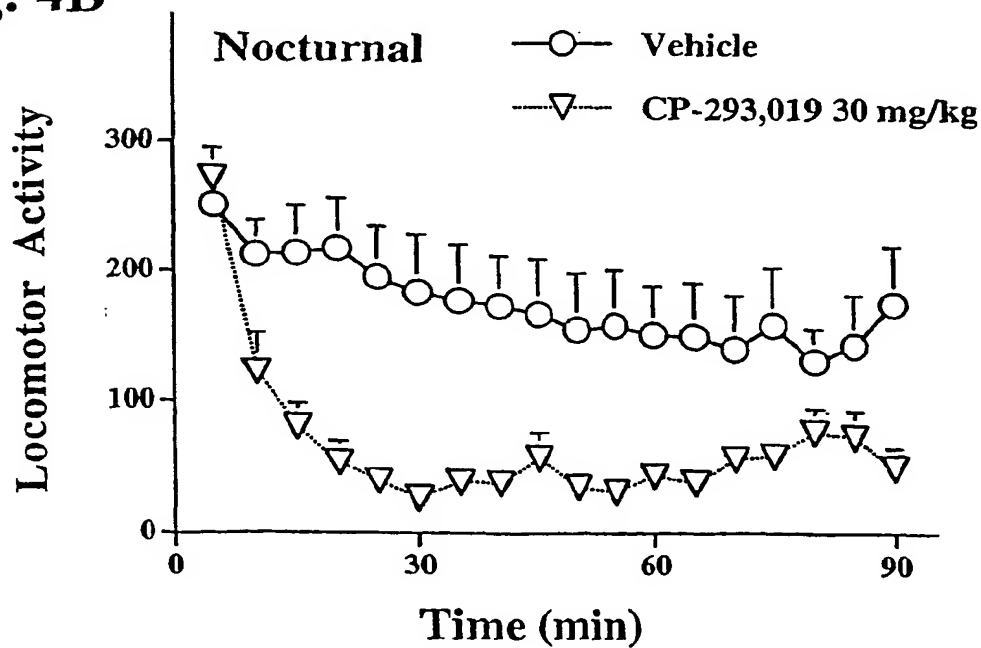
Fig. 4A**Fig. 4B**

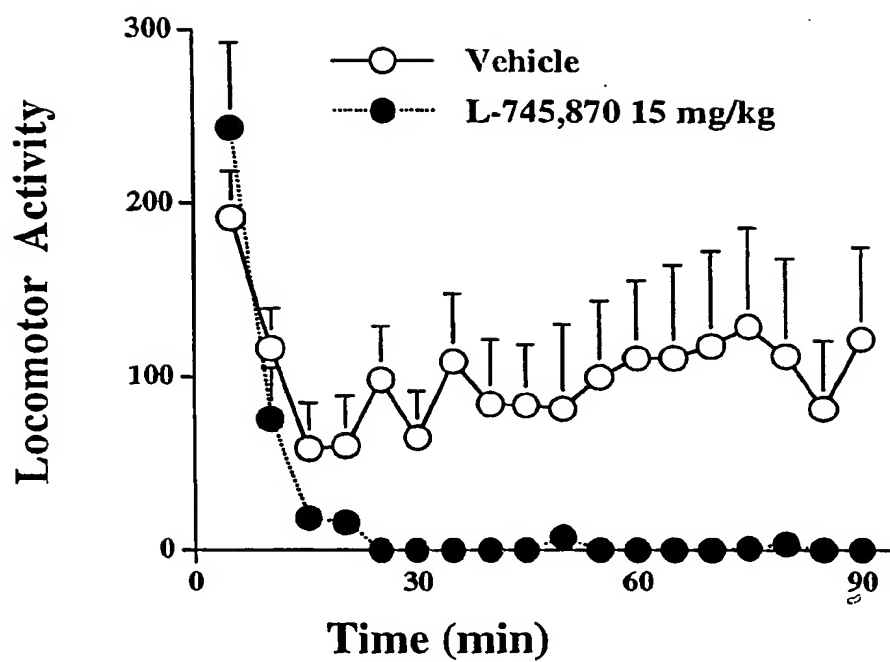
Fig. 5

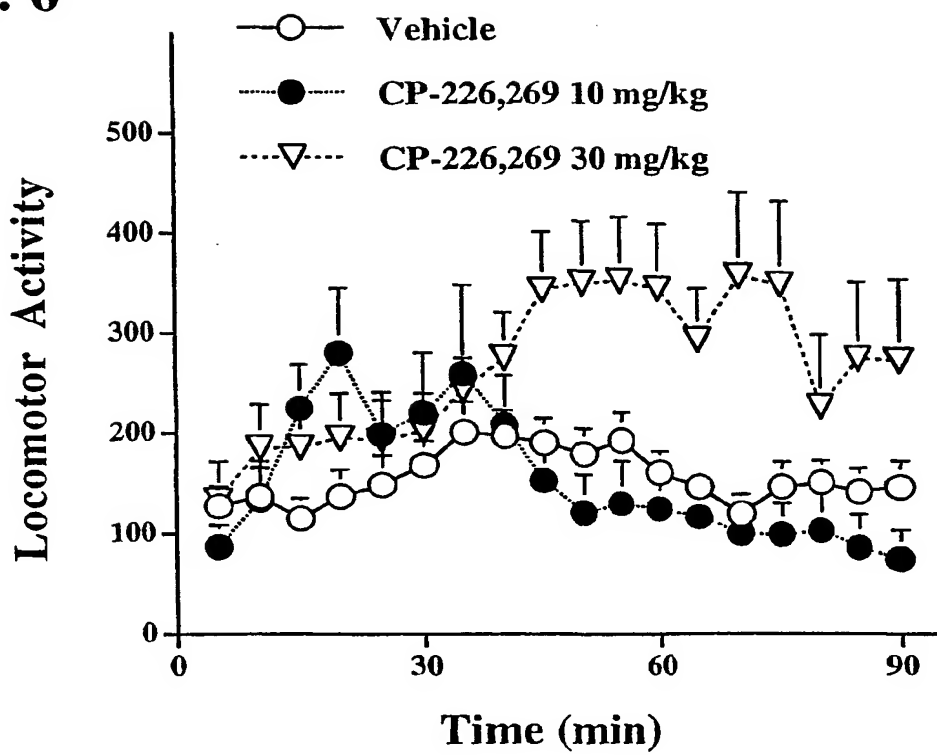
Fig. 6

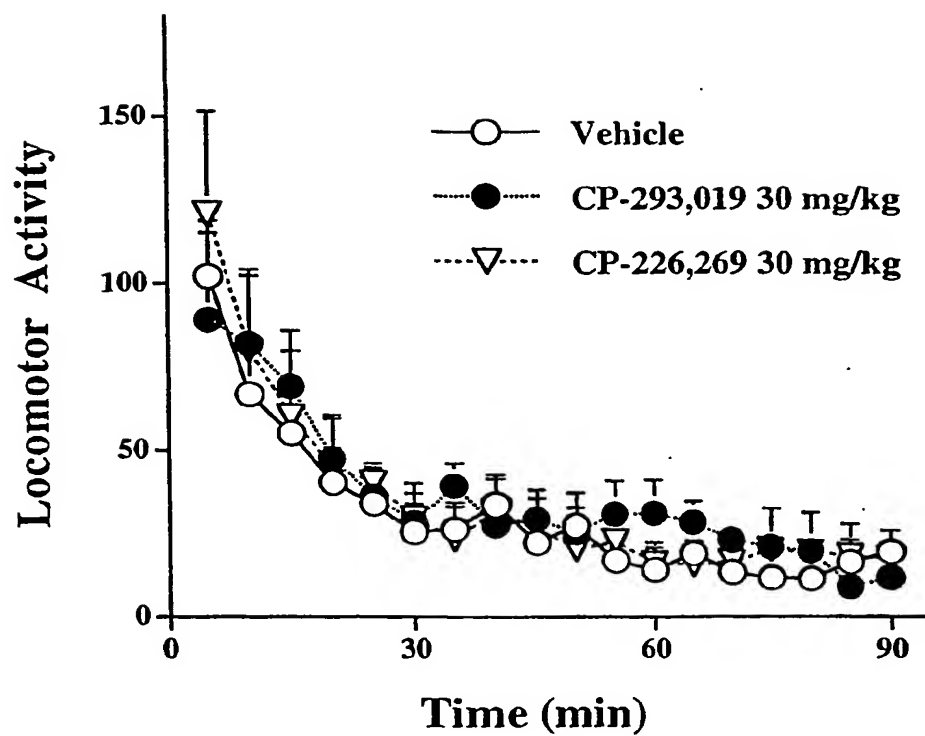
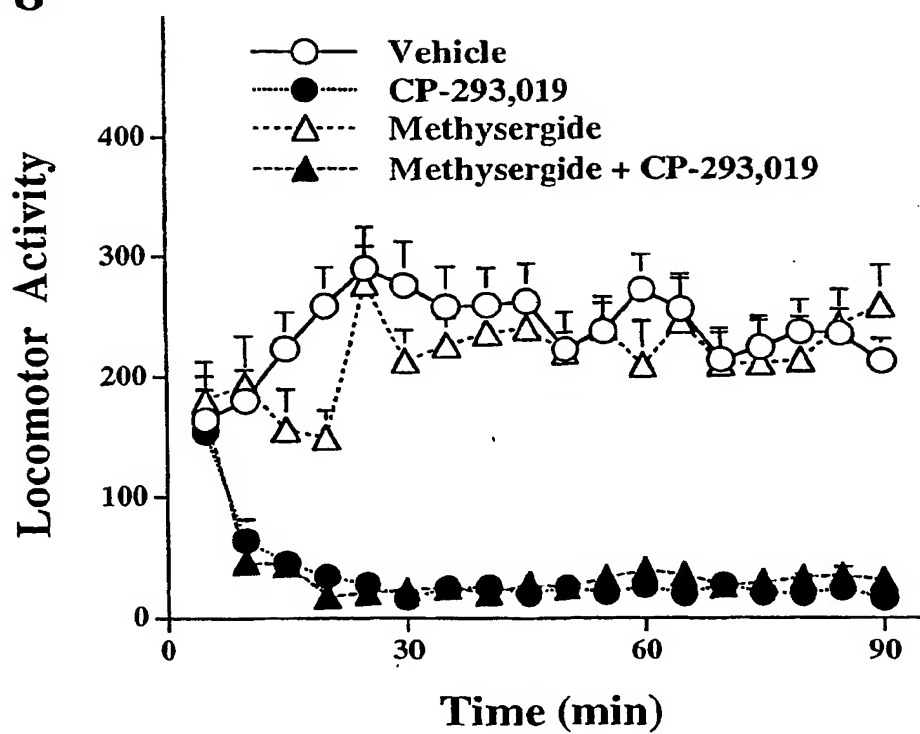
Fig. 7

Fig. 8

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(57) Abstract: A method of inhibiting motor hyperactivity in a mammal exhibiting the symptoms of attention deficit-hyperactivity disorder (ADHD) includes administering to a mammal a dopamine D₄ receptor-selective antagonist.



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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
Y	ZHUANG et al, Hyperactivity and impaired response habituation in hyperdoperminergic mice. Proc Natl Acad Sci U S A. 13 February 2001, Vol. 98, No. 4, pages 1982-1987, see entire document.	1-9										
Y	KULA et al, Neuropharmacological assessment of potential dopamine D4 receptor-selective radioligands. European Journal of Pharmacology. 1999, Vol. 367, pages 139-142, see entire document.	1, 3-6, 8-9										
Y	US 5,576,319 A (BAKER et al) 19 November 1996, see entire document.	1, 4, 5, 6, 9										
Y	FARACI et al, The discovery of potent and selective dopamine D4 receptor antagonists. Current Opinion in Chemical Biology 1998, Vol. 2, No. 4, pages 535-540, see entire document.	1-9										
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